Review article

Peanut and soy allergy: a clinical and therapeutic dilemma

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Peanut and soy share several characteristics that are relevant to allergy. First, as legumes, they are phylogenetically and antigenically (1, 2) similar to each other and to other beans. Second, they are common sources of protein in the food supply; therefore, exposure to them is widespread. Third, they are an exceedingly common cause of food allergy (3–7). While these two food allergens have much in common, the clinical manifestations of allergy to peanut and soy are generally quite distinct. This paper will explore the similarities and differences in the clinical manifestations of peanut and soy allergy, summarize the current understanding of the molecular-immunologic aspects of these allergies, and discuss recent concerns regarding the development of severe allergy to soy in peanut-allergic individuals.

Characteristics of peanut allergy

Prevalence

Recent surveys of the general population found the prevalence of peanut allergy to be 0.48% in the UK (7) and 0.6% in the USA (3). Peanut is ubiquitous within the US food supply, with virtually 100% of US children being exposed by the age of 2 years (8). The sensitization

rate to peanut in a birth cohort of children on the Isle of Wight, UK, followed to the age of 4 years, was 1%, with half having experienced a clinical reaction to peanut (9). In children with atopic dermatitis undergoing evaluation for food hypersensitivity, 20/113 (18%) (5) and 27/165 (16%) (4) were allergic to peanut.

Clinical manifestations

The clinical characteristics of peanut allergy have been explored from a variety of vantage points. Studies of peanut-allergic individuals have highlighted the acute and severe nature of the allergy. In our study of 101 children (median age 7.6 years) with acute reactions to peanut (10), reactions occurred soon after ingestion, with 91% experiencing skin symptoms, 45% respiratory symptoms, and 36% gastrointestinal symptoms. In this group, 47% had involvement of two or more organ systems and 20% required treatment with epinephrine for their first reaction. A study of 622 peanut-allergic individuals in the UK (11) also highlighted the severity of reactions because over 50% had moderate to severe reactions with breathing difficulties or cardiovascular collapse. Severe symptoms were more common in adults than young children. A review of a referral population of 142 peanut-allergic individuals in France

by Moneret-Vautrin et al. (12) also highlighted the severity of peanut allergy in that 87.5% reacted to a dose of peanut under 1 g in oral challenges, and 25% reacted to doses under 100 mg. Studies of unreferred peanut-allergic individuals from the general population also indicate the severity of this allergy. Our population-based study of peanut allergy (3) disclosed a high proportion of severe symptoms: throat tightness (56%), dyspnea (43%), wheezing (36%), angioedema (51%), urticaria (42%), vomiting (18%), diarrhea (14%), and loss of consciousness (4%). One organ system (skin, respiratory, or gastrointestinal) was affected in 42%, two systems in 38%, and all three systems in 20%. Similarly, the population-based study in the UK revealed severe reactions with a hospitalization rate of 7.4% (7). The prominence of peanut as a cause of severe allergic reactions has been shown in case series of anaphylaxis (13–15) and in case series of fatal, food-allergic reactions (16, 17) (Table 1).

Natural history

Allergy to peanut generally does not remit, and affects adults and children at a similar rate (3, 7). Bock & Atkins (18) followed 32 peanut-allergic children (confirmed by double-blind, placebo-controlled oral food challenges) aged 1–14 years (mean, 7 years) for a mean of 7 years, and found that none had a remission. All of the subjects also maintained a positive prick skin test to peanut. In contrast to these findings, Golding et al. (19) found that 41% of 22 children from a birth cohort of 14 210 in the UK with peanut allergy identified before the age of 2 years by clinical histories had outgrown their allergy by the age of 5 years. Hourihane et al. (20) have also shown that peanut allergy may resolve in young children when the allergy was first manifested in infancy. This group evaluated 22 children with resolved peanut allergy culled from 120 of 230 with peanut allergy who underwent an oral challenge to peanut. In contrast to Bock & Atkins's cohort, this group experienced a reaction at a mean of only 11 months of age. In a case–

control comparison of a group of 15 who experienced resolution to a group that did not, the former group had smaller or negative prick skin tests, no recent reactions from accidental ingestions, and less atopic disease. Taken together, these studies indicate that infants may become tolerant, but once the allergy is established in early childhood, resolution is rare.

Characteristics of soy allergy

Prevalence

Soy is a common source of dietary protein and is introduced into the diet early in life, often in the form of infant formula, particularly in infants with intolerance or allergy to cow's milk-based formula. The prevalence of soy allergy has not been specifically studied. In a population-based study by Young et al. of food intolerance in the UK (21), soy was the least frequent cause of food intolerance (0.3%) among 16 foods/food types reported. In a study of food allergy/intolerance in a cohort of 480 neonates, two (0.4%) developed soy allergy as infants (22). Among children with atopic dermatitis examined for food hypersensitivity, 5/113 (4.4%) (5) and 3/165 (1.8%) reacted to soy. In a multicenter study in Italy (23), reactions to soy were documented in 6/505 (1.2%) of children with a history suggestive of food allergy, and in 1/243 (0.4%) of children at risk of atopy fed soy-based infant formula for allergy prophylaxis.

Magnolfi et al. (24) performed oral challenges with soy in 131 children with a positive skin prick test to soy, and only 6% reacted (representing 1.1% of children referred for atopic diseases). In a study utilizing blinded challenges, among infants with IgE-mediated cow's milk allergy, 13/93 (14%) reacted to soy (25). While this study specifically addressed the rate of IgE-mediated reactions to cow's milk and soy, there has been no study addressing the rate of immune-mediated gastrointestinal reactions to soy that occur without evidence of soy-specific IgE antibody. One example of this disorder is food-protein-induced enterocolitis syndrome. This disorder is characterized by delayed (hours) vomiting and diarrhea with elevation of the serum polymorpho-nuclear leukocyte count after ingestion of the causal food protein (26–28). Some patients experience severe dehydration, failure to thrive, and shock (26, 29, 30). Less severe forms of food-induced enteropathy may also occur. Among infants with these reactions to cow's milk protein, approximately 50% also react to soy (27, 28).

Clinical manifestations

The clinical manifestations of soy allergy are broad, ranging from the syndrome of severe enterocolitis of infancy, as mentioned above, to immediate, multisystem IgE-mediated reactions. However, the impression has

Table 1. Frequency of severe reactions caused by peanut and soy

Population	Total food allergic	Number reacting to peanut	Number reacting to soy
Fatal			
Case series (USA) (16)	7	4	0
Case series (USA, children) (17)	6	3	0
Case series (Sweden, children) (33)	6	2	4
Anaphylaxis, not fatal			
Anaphylaxis (northwest England) (15)	90	42	2
Anaphylaxis (USA) (14)	89	20	0
Anaphylaxis (USA) (13)	18	4	0
Anaphylaxis (France) (32)	60	7	2
Anaphylaxis (Singapore, children) (31)	124	0	0

been that, unlike peanut allergy, soy allergy is not responsible for severe, life-threatening reactions. Table 1 compares the rate of peanut and soy allergy in studies of anaphylaxis and fatal, food-induced reactions. The rate of anaphylaxis and fatal reactions caused by these two foods was zero in Singapore (31) but more common in the USA and Europe (14–17, 32, 33). As stated, soy has not been shown to be a common cause of severe/fatal reactions until a recent report of severe food-allergic reactions in Sweden collected by Foucard & Malmheden Yman (33), which will be discussed below.

Natural history

The natural history of soy allergy indicates that it is generally a transient allergy of infancy/childhood. In the study by Bock (22), all of the allergic infants became tolerant of soy by the age of 3. In the study by Sampson & McCaskill (5), two-thirds lost their soy allergy 2 years after a positive oral challenge. In a prospective study of Danish children with cow's milk allergy (34), 5.1% demonstrated soy allergy in infancy, but all the cases had resolved by the age of 3 years.

Clinical studies on coallergy to peanut and soy

Since there are homologous proteins in peanut and soy, it is not uncommon to find positive tests for IgE antibody to both of these foods in individuals who are clinically reactive to one or the other. Using RAST and RAST inhibition, Barnett et al. (1) showed that peanut-allergic individuals had extensive IgE binding to other legumes, including soy. Their recommendations, based upon these *in vitro* studies, to avoid other legumes in peanut-allergic individuals were questioned (35). In fact, clinical observations had shown a surprisingly low rate of coreactivity to peanut and soy. For example, among 113 children with atopic dermatitis, only one (0.8%) had food allergy to both foods (5), a low rate that was confirmed later (3/165 [1.8%]) (4) in a similar population. Bock & Atkins (18) studied 32 children with peanut allergy confirmed by double-blind, placebo-controlled oral food challenges, and found that 10 had a positive skin test to soy, but only one (3%) had a clinical reaction upon ingestion of soy.

In a larger study, Bernhisel-Broadbent & Sampson (2) specifically addressed the clinical relevance of the cross-reactivity among legumes. These investigators performed open or double-blind, placebo-controlled food challenges in 69 highly atopic children (median age 5 years; range, 1–21 years) with at least one positive skin test to a legume. Eighty-seven percent had a positive skin test to peanut, and 43% to soy. After challenges to five legumes, 43 positive reactions occurred in 41 patients (59%). Thirty-one were challenge-positive/anaphylaxis-history reactions to peanut. Only two of the 31 patients (6.5%) with severe peanut allergy had reactions to soy,

and these were mild. Thus, 6.5% of the peanut-allergic children reacted to soy. These two patients lost their soy sensitivity after 3 years and were also able to consume other legumes. Conversely, eight soy-reactive children tolerated peanut. The authors concluded that elimination of all legumes in individuals with clinical reactions to one legume was unwarranted despite the high prevalence of multiple legume-positive skin tests.

The recent report of severe food-allergic reactions in Sweden has raised new concern over soy allergy in peanut-allergic individuals (33). These investigators reviewed the medical records of all fatal or life-threatening reactions sent to them by physicians in Sweden over a 3-year period. They also reviewed records from a concurrent study on fatal asthma and included data on known deaths caused by food allergy in the year before the prospective study. In 1993–6, 61 cases of severe reactions to food were reported, four of them fatal. After review, the authors considered 12 cases to be severe/life-threatening (required intensive care), and these were caused by (not confirmed) soy (six patients), peanut (four), egg, and Brazil nut. The patients were aged 3–21 years, and all, except possibly one, had a diagnosis of allergy to the food ingested accidentally. In assessing fatal reactions, the authors included two cases that occurred less than 1 year before the study began. In all, two deaths caused by peanuts and four deaths presumably caused by soy were evaluated. These subjects were aged 9–18 years, and all had severe asthma and known severe peanut allergy, but no reaction to previous soy ingestion. Among the severe reactions, the foods responsible for reactions in the soy-allergic individuals were hamburger (two patients), kebab (one), ice cream (two), and soy sauce (one). In the four fatal reactions in peanut-allergic individuals who apparently reacted to soy despite previous tolerance, the causal foods were hamburger in three cases (2.2–3% soy) and kebab in one case (7% soy). Most of the children had high peanut-specific IgE and "moderate" soy-specific IgE. In two out of the four cases of peanut-allergic children reacting to soy, the gastric contents were available and were analyzed for peanut protein. Testing did not reveal peanut protein, but did, reportedly, reveal soy. The authors concluded that soy allergy has probably been underestimated as a cause of food anaphylaxis, and that those at risk seem to be young people with asthma and peanut allergy so severe that they notice symptoms after infinite contact. The findings have raised concern among patients with peanut allergy and their physicians. However, there are several limitations of this study that will be discussed below.

Molecular aspects of peanut and soy allergy

One important way to study the relevance of cross-reactive proteins is through careful molecular and

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Table 2. Progress in characterizing particular peanut and soy allergens

Protein	Family	Molecular mass (kDa)	IgE epitopes mapped	T-cell epitopes mapped	Mutational analysis	cDNA
Peanut						
Ara h 1	Vicilin	63.5	23, four dominant	Underway	Yes	Isolated, expressed
Ara h 2	Conglutin	17.5	10, three dominant	Four dominant, three unique from IgE	Yes	Isolated, expressed
Ara h 3	Glycinin	60	Four, one dominant		Yes	Isolated, expressed
Soy						
Gly m 1	Conglycinin, N-terminal sequence identical to P34, a thiol protease	30	16, five immunodominant		Underway	
G2 glycinin	Glycinin	21	Underway		Underway	Isolated, expressed

immunologic analysis of the causal proteins. Such studies may lead to better diagnostic and therapeutic approaches. In the past decade, significant advances have been made in identifying the allergenic proteins in peanut and soy and in determining the immunologic properties of these proteins. Table 2 summarizes the progress in this area. These legumes contain water-soluble (albumins) and salt-soluble (globulin) protein fractions that each contain allergenically significant proteins.

Crossed-radioimmunoelectrophoresis (CRIE) has identified 16 allergenic fractions in raw peanut (36), and SDS-PAGE has revealed 32 protein bands. Three major allergens have been identified: Ara h 1 (64.5 kDa, vicilin family of seed storage proteins) (37), Ara h 2 (17.5 kDa, conglutin family of seed storage proteins) (38), and Ara h 3 (60 kDa, glycinin-like seed storage protein, a preproglobulin) (39). By using soy-absorbed, peanut-allergic patient sera on two-dimensional immunoblots and N-terminal amino-acid sequencing, about 30 protein fractions were shown to be isoforms, or fractions, of the three major peanut proteins (40). Studies on the biochemical, structural, and immunologic characteristics of these proteins, using native proteins or cDNA clones and allergic sera, have further elucidated important features of these proteins with implications for therapeutic intervention (39, 41–46). For example, Ara h 1 forms a stable trimer that may add stability to the protein, an important characteristic of allergens (43). Furthermore, epitope analysis reveals that linear, as opposed to conformational epitopes, are prominent; however, single amino-acid substitutions of IgE-binding sites often lead to a loss of binding to these epitopes, a finding with obvious therapeutic implications (39, 43, 46, 47).

Investigations of soy proteins have also identified numerous protein fractions by ultracentrifugation: 2S (alpha-conglycinin composed of 18.2- and 32.6-kDa fractions), 7S (beta-conglycinin that exists as a trimer or hexamer in solution with a monomeric form of 150–170 kDa), 11S (glycinin 320–350-kDa protein composed of 12 subunits), and 15S (aggregated glycinin). While some studies identified no major allergenic fraction (48), others suggested that the 2S

fraction (49) or the 7S fraction (50) contains significantly allergenic proteins. Identification and epitope analysis of allergenic soy proteins are well underway. Gly m 1, a 30-kDa protein, was characterized in the 7S fraction of soy extract (50, 51) and had a frequency of IgE binding of 65.2% among 69 soy-allergic patients. Specific linear IgE-binding epitopes have recently been identified, and mutational analysis is underway.

Investigations to clarify the clinical relevance of unique and homologous proteins in these legumes are underway. Immunoblots using sera from soy-allergic individuals tolerant of peanut were found to bind soy protein with a mass of 20 kDa (52). In another study, peanut antigen preabsorption of sera from soy-allergic children to remove peanut cross-reactive proteins identified two unique allergenic fractions of soy with masses of 40 and 21 kDa, and seven unique peanut fractions were identified when soy cross-reactive antibodies were absorbed out of sera from peanut-allergic subjects (53). Taken together, these studies have indicated the presence of unique peanut and soy-allergenic proteins. Further studies on homologous proteins are underway. Preliminary data (unpublished) indicate that despite homology in protein sequences among Ara h 1, Ara h 3, and soy glycinin, the IgE-binding sequences in these proteins are distinct.

Final comments

Over a decade ago, studies demonstrated that most peanut-allergic patients could ingest other legumes safely. The recent report of Foucard & Malmheden Yman (33) suggests that fatal reactions to soy may occur in highly peanut-allergic, presumably soy-tolerant, individuals exposed to soy protein. In addition to the above studies, the lack of concern regarding the ingestion of other legumes in peanut-allergic patients was based on the rarity of severe soy allergy and the transient nature of soy allergy, as reviewed above. Should allergists now advise peanut-allergic individuals to avoid soy or other legumes?

The first question in addressing this issue is: does the potential cross-reactivity of peanut and soy truly increase the risk of a reaction? The clinical studies

cited above showing the low prevalence of soy allergy and its transient nature indicate that this is not the case. In series of food-allergic individuals, allergy to multiple foods is usually due to reactions to botanically unrelated, classically allergenic foods (e.g., peanut, egg, milk, tree nuts). It appears that highly atopic individuals are most likely to react to the most highly allergenic foods (for their age group). This issue of coallergy has been demonstrated in several recent studies. In our referral group of peanut-allergic children, 57% had (transient) egg hypersensitivity (10), and Ewan (54) noted that 30% of her referral population had both peanut and tree nut allergy. Outside referral populations, coallergy is less common; population-based studies show coallergy to peanut and tree nuts to be uncommon (2.4%) (3). While there are increasing reports of allergy to legumes such as lentil and lupine (55–57), more work is needed to characterize the role of cross-reactive proteins in the risk of clinical coallergy. This issue has been raised for lupine, which appears to be an allergenic food in peanut-allergic patients. A major allergen in lupine flour (43 kDa) was identified, and there was complete inhibition of immunoblot lupine flour by peanut (55). However, this protein is not known to be a major allergen in peanut, and so more work is needed to determine coallergy versus cross-reactivity as the relevant issue.

The second consideration in applying the findings of Foucard & Malmheden Yman (33) to peanut-allergic patients is the nature of the case studies. Apparently, all of the fatal reactions to soy occurred in peanut-allergic, soy-tolerant children. Is it possible that these children developed a new soy allergy, or was there some occult, possibly minute, peanut exposure of these highly peanut-allergic individuals? In two instances, the gastric contents were analyzed and did not show peanut protein, but did reveal soy protein. No specific information on the specificity of the assay was given

in the paper, but considering the difficulty of measuring specific proteins in foods and the difficulty of generating peanut-specific and soy-specific detection antibodies, it remains uncertain whether the assays utilized could accurately exclude the presence of small amounts of peanut protein in gastric contents. Were monoclonal antibodies to peanut-specific epitopes used in the assay? Another curiosity in the case series was that the foods causing the reactions were remarkably similar to each other and to those causing severe reactions in three other peanut-allergic children in the report: ground beef and kabab with "soy" protein added. Were these particular foods contaminated with trace quantities of peanut protein, lupine, or some other allergen? Could soy flours used for these particular foods be contaminated with peanut protein? Finally, it is striking that these authors identified more fatal soy-allergic reactions in a single country than have been reported in the rest of the world.

There are many unanswered questions in food allergy, and the issues of cross-reacting proteins and botanically related foods, and the significance of positive tests for IgE (prick skin test, RAST) are all at work in the dilemma of peanut and soy allergy. Half of the 4-year-old children in the birth cohort on the Isle of Wight (9) had positive peanut prick skin tests but had not yet experienced a reaction – will they ever do so? Should they avoid peanut? Should they avoid soy? Most allergists would not stop an individual from ingesting a tolerated food on the basis of a positive prick skin test; in fact, demonstration of the ability to ingest the food is the basic proof of tolerance! It does not appear that we have enough data to recommend soy avoidance in soy-tolerant, peanut-allergic patients at this time. Further studies on the natural history of these allergies and on the molecular-immunologic features of these proteins will undoubtedly shed more light on these issues in the coming years.

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